Using human pluripotent stem cell-derived dopaminergic neurons to evaluate candidate Parkinson's disease therapeutic agents in MPP+ and rotenone models.

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Public Summary:
To begin to develop a high-throughput assay system to evaluate potential small-molecule therapy for Parkinson's disease (PD), we have performed a low-throughput assay with a small number of compounds using human pluripotent stem cell-derived dopaminergic neurons. We first evaluated the role of 44 compounds known to work in rodent systems in a 1-methyl-4-phenylpyridinium (MPP(+)) assay in a 96-well format using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay as a readout for neuroprotection. Glial cell-derived neurotrophic factor was used as a positive control because of its well-documented neuroprotective effect on dopaminergic neurons, and two concentrations of each drug were tested. Of 44 compounds screened, 16 showed a neuroprotective effect at one or both dosages tested. A dose-response curve of a subset of the 16 positives was established in the MPP(+) model. In addition, we validated neuroprotective effects of these compounds in a rotenone-induced dopaminergic neuronal cell death, another established model for PD. Our human primary dopaminergic neuron-based assays provide a platform for rapid screening and/or validation of potential neuroprotective agents in PD treatment using patient-specific cells and show the importance of using human cells for such assays.

Scientific Abstract:
To begin to develop a high-throughput assay system to evaluate potential small-molecule therapy for Parkinson's disease (PD), we have performed a low-throughput assay with a small number of compounds using human pluripotent stem cell-derived dopaminergic neurons. We first evaluated the role of 44 compounds known to work in rodent systems in a 1-methyl-4-phenylpyridinium (MPP(+)) assay in a 96-well format using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay as a readout for neuroprotection. Glial cell-derived neurotrophic factor was used as a positive control because of its well-documented neuroprotective effect on dopaminergic neurons, and two concentrations of each drug were tested. Of 44 compounds screened, 16 showed a neuroprotective effect at one or both dosages tested. A dose-response curve of a subset of the 16 positives was established in the MPP(+) model. In addition, we validated neuroprotective effects of these compounds in a rotenone-induced dopaminergic neuronal cell death, another established model for PD. Our human primary dopaminergic neuron-based assays provide a platform for rapid screening and/or validation of potential neuroprotective agents in PD treatment using patient-specific cells and show the importance of using human cells for such assays.